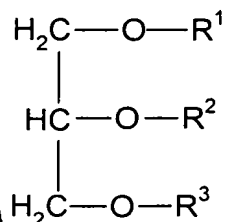


CLAIMS

1. A pharmaceutical formulation comprising at least one bisphosphonate and one or more of an additive agent, said additive agent being present in an amount sufficient to provide an enhanced absorption of the bisphosphonate, and said additive being a substance selected from the group consisting of

- a surfactant;
- an ampholytic surfactant;
- an anionic surfactant;
- a cationic surfactant;
- a bile salt;
- a soap and a fatty acid, and a salt thereof;
- a lipid with the exception of a medium chain glyceride or a mixture of medium chain glycerides having the formula



wherein R^1 , R^2 and R^3 are the same or different and each represent a hydrogen atom or an alkanoyl chain having 6 to 18 carbon atoms, preferably 6 to 12 carbon atoms, provided that at least one of R^1 , R^2 and R^3 is an alkanoyl group.

- an oil;
- an enamine;
- a chelating agent;
- a phenothiazine;
- a fatty acid derivative of carnitine or a peptide;
- a substance selected from the group consisting of azone, concanavalin A, a phosphate and a phosphonate derivative, such as DL - α -glycerophosphate and 3-amino-1-hydroxypropylidene-1,1-diphosphonate, diethyl maleate and diethylethoxymethylene malonate;

SubA'ant
- a product from Maillard reactions;

- a polymer, such as a block copolymer and a biodegradable polymer;
- a chitosan and a chitosan derivative;

5 2. A pharmaceutical formulation according to claim 1, wherein the additive is a nonionic surfactant.

3. A pharmaceutical formulation according to claim 2, wherein the nonionic surfactant is a sugar glycoside or a sugar fatty acid ester.

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4. A pharmaceutical formulation according to claim 1, wherein the additive is a lipid.

5. A pharmaceutical formulation according to claim 4, wherein the lipid is a phospholipid.

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6. A pharmaceutical formulation according to claim 1, wherein the additive is an oil.

7. A pharmaceutical formulation according to claim 6, wherein the oil is soy bean oil or sunflower oil.

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8. A pharmaceutical formulation according to claim 1, wherein the additive is a chelating agent.

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9. A pharmaceutical formulation according to claim 8, wherein the chelating agent is EDTA, EGTA or citric acid.

10. A pharmaceutical formulation according to claim 1, wherein the additive is a fatty acid derivative of carnitine or a peptide.

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11. A pharmaceutical formulation according to claim 10, wherein the additive of the fatty acid derivative of carnitine or a peptide is palmitoyl-DL-carnitine.

Substantive 12. A pharmaceutical formulation according to claim 1, wherein the additive is a polymer.

13. A pharmaceutical formulation according to claim 12, wherein the polymer is a polyacrylic acid.

14. A pharmaceutical formulation according to claim 1, wherein the additive is a block copolymer.

15. A pharmaceutical formulation according to claim 14, wherein the block copolymer is a poloxamer, a poloxamine or meroxapol.

16. A pharmaceutical formulation according to claim 1, wherein the additive is a saponin.

17. A pharmaceutical formulation according to claim 1, wherein the additive is a biodegradable polymer.

18. A pharmaceutical formulation according to claim 17, wherein the biodegradable polymer is polyactid acid or polyglycolic acid.

19. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid and a surfactant.

20. A pharmaceutical formulation according to claim 19, wherein the combination of the lipid and the surfactant is monoolein and sodium taurocholate, or monoolein and Tween 80.

21. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid of non-phospholipid character and a phospholipid.

22. A pharmaceutical formulation according to claim 21, wherein the combination of the lipid of non-phospholipid character and the phospholipid is a medium chain glyceride and a lecithin.

Sub Alcant 23. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid and a block copolymer.

5 24. A pharmaceutical formulation according to claim 23, wherein the combination of the lipid and the block copolymer is monoolein and Pluronic F 127.

25. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a surfactant and an oil.

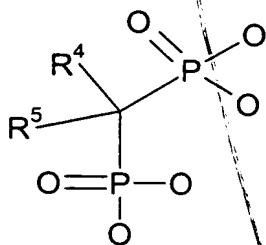
10 26. A pharmaceutical formulation according to claim 25, wherein the combination of the surfactant and the oil is a sucrose fatty acid ester and soy bean oil.

15 27. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a polymer and a lipid.

28. A pharmaceutical formulation according to claim 27, wherein the combination of the polymer and the lipid is polycarbophil and monolein.

20 29. A pharmaceutical formulation according to claim 1, wherein the combination of additives is chosen to form an emulsion or a microemulsion.

25 30. A pharmaceutical formulation according to any one of claims 1 to 29 wherein the said bisphosphonate has the formula II



II

wherein

Sub A1008
R⁴ is H, OH or Cl, and

R⁵ is

- (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- (b) halogen;
- (c) arylthio or chlorosubstituted arylthio;
- (d) cycloalkylamino with 5 to 7 carbons; or
- (e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

31. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate has the formula II

wherein

R⁴ is H or OH and

R⁵ is

- (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- (d) cycloalkylamino with 5 to 7 carbons; or
- (e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

32. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate has the formula II

wherein

R⁴ is OH and

R⁵ is

- (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- (d) cycloalkylamino with 5 to 7 carbons; or
- (e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

- Sub Alcant
33. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate), N,N-dimethyl-3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (mildronate, olpadronate), 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid (ibandronate), 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid (risedronate), 1-hydroxyethylidene-1,1-bisphosphonic acid (etidronate), 1-hydroxy-3-(1-pyrrolidiny)propylidene-1,1-bisphosphonic acid, 1-hydroxy-2-(1-imidazolyl)ethylidene-1,1-bisphosphonic acid (zoledronate), 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene-1,1-bisphosphonic acid (minodronate), 1-(4-chlorophenylthio)methylidene-1,1-bisphosphonic acid (tiludronate), 1-(cycloheptylamino)methylidene-1,1-bisphosphonic acid (cimadronate, incadronate), 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate) and pharmaceutically acceptable salts thereof.
34. A pharmaceutical formulation according to claim 33 wherein the bisphosphonate is alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid) or pharmaceutically acceptable salts thereof.
35. A pharmaceutical formulation according to any one of claims 1 to 34 which is adapted for oral administration.
36. A pharmaceutical formulation according to any one of claims 1-35 which is adapted for non colonic delivery.
37. A pharmaceutical formulation according to any one of claims 1 to 36 for inhibiting bone resorption.

38. A pharmaceutical formulation according to any one of claims 1 to 36 for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis.

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Sub A2 39. A pharmaceutical formulation according to any of the preceding claims wherein the formulation is in particulate form.

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40. A pharmaceutical formulation according to claim 39 wherein the particulate form is solid or semisolid.

41. A pharmaceutical formulation according to any of claims 39 and 40 wherein the bisphosphone is in the form of micronized powder.

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42. A process for the preparation of a pharmaceutical formulation according to any one of claims 1 to 40, comprising forming a mixture of (i) at least one bisphosphonate, (ii) an additive and (iii) a pharmaceutically acceptable carrier.

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43. The use of a pharmaceutical formulation according to any one of claims 1 to 41 for the manufacture of a medicament for the inhibition of bone resorption.

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44. The use of a pharmaceutical formulation according to any one of claims 1 to 41 for the manufacture of a medicament for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, or cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis.

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Sub A3 45. A method for inhibition of bone resorption which comprises administering to a mammal, including man, in need of such treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 41.

§

- Abstract**

✓ Add A4

اسم	تاريخ الميلاد	تاريخ الوفاة	مكان الميلاد	مكان الوفاة
أحمد بن محمد	1234	1298	بغداد	بغداد
علي بن علي	1245	1310	بغداد	بغداد
محمد بن أحمد	1256	1325	بغداد	بغداد
علي بن محمد	1267	1335	بغداد	بغداد
أحمد بن علي	1278	1345	بغداد	بغداد
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علي بن محمد	1923	1995	بغداد	بغداد
أحمد بن علي	1934	2005	بغداد	بغداد
محمد بن علي	1945	2015	بغداد	بغداد
علي بن أحمد	1956	2025	بغداد	بغداد
أحمد بن محمد	1967	2035	بغداد	بغداد
محمد				